

REMARKS

Claim Status

Upon entry of the claim amendment and additions herein, Claims 1, 3, 5 – 8, and 11 – 21, and 24 – 45 will be pending. Claims 13 – 15 and 24 – 45 have been withdrawn from consideration.

Claim 1 has been amended to recite methods of determining the efficacy of a *probiotic* as a treatment of inflammatory diseases of the bowel in mammals. Support for this amendment is found in the specification at pages 9 and 14 – 17, and throughout.

Claims 22 and 23 have been canceled.

No new matter has been added. Thus, entry and consideration of the amendments is respectfully requested.

The Rejection Under 35 USC § 112, Second Paragraph

Claims 22 and 23 have been rejected under 35 USC § 112, Second Paragraph. These claims have been canceled. As such, the rejection is moot and should be withdrawn.

The Rejection Under 35 USC § 112, First Paragraph

Claims 1, 3, 5-8, 11, 12 and 16-21 have been rejected under 35 USC § 112, First Paragraph. Applicants have amended independent Claim 1 to recite methods of determining the efficacy of a *probiotic* as a treatment of inflammatory diseases of the bowel in mammals. Dependent Claims 3, 5-8, 11, 12 and 16-21 are affected by this amendment. Support for this amendment is found in the specification at pages 9 and 14 – 17, and throughout.

Applicants therefore assert that the rejection of Claims 1, 3, 5-8, 11, 12 and 16-21 have been overcome. Thus, the Applicants respectfully request withdrawal of the rejection.

The Rejections Under 35 USC § 102(b)

Claim 22 has been rejected under 35 USC § 102(b). This claim has been canceled. As such, the rejection is moot and should be withdrawn.

*The Rejections Under 35 USC § 103(a)*

Claim 23 has been rejected under 35 USC § 103(a). This claim has been canceled. As such, the rejection is moot and should be withdrawn.

*Towaga*

Claims 1, 3, 5, 16, 17, 19, and 20 have been rejected under 35 USC § 103(a) in view of Towaga *et al.*, 2002 Am J. Physiol, Gastrointestinal Liver Physiol 283:G187-G195 (“Towaga”).

As amended herein, Claim 1 is directed to methods of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. As the Examiner acknowledges, Towaga teaches administration of TNBS to induce colitis and studies the use of lactoferrin to attenuate the induced colitis. As such, the rejection is now moot since fails to teach or suggest methods to determine the efficacy of probiotics in inflammatory diseases of the bowel.

Additionally, the Examiner acknowledges that Towaga does not teach measuring cytokine levels before and after treatment *or* determining the ratios of cytokines before and after treatment. Towaga details only one particular experiment in rats using induced colitis. Towaga does not provide any suggestion or motivation to study ‘before and after’ results, or to set up such experiments, without controls. Towaga does not suggest studying ratios of cytokines to establish and analyze shifts in patterns of cytokine levels to evaluate efficacy of treatment. In particular, Towaga does not suggest or provide motivation for the particular cytokines and ratios as set forth in the claims. Towaga simply induces colitis in rats and compares cytokine levels to those of normal, control rats in conjunction with studying physical aspects of the induced disease such as thickness of the colon, weight of the colon, and presence and size of lesions, in order to determine whether lactoferrin is effective against the induced colitis.

Therefore, Applicants submit that the disclosure of Towaga fails to teach or suggest the claimed invention as amended herein with respect to determining the efficacy of a probiotic in particular, and that one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga. Therefore, Applicants assert that the rejection has been overcome.

*Towaga in view of Vignali*

Claims 18 and 21 have been rejected under 35 USC § 103(a) based on Towaga in view of Vignali.

As amended herein, Claim 1 is directed to methods of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. Claims 18 and 21 are dependent upon Claim 1 and are therefore affected by this amendment. As the Examiner acknowledges, Towaga teaches administration of TNBS to induce colitis and studies the use of lactoferrin to attenuate the induced colitis. As such, the rejection is now moot since fails to teach or suggest methods to determine the efficacy of probiotics in inflammatory diseases of the bowel.

Additionally, Applicants maintain that one of ordinary skill in the art would not have been motivated to make the jump from one type of rat study to a different type of human study, simply because clinical study techniques are generally known, even if Towaga were combined together with Vignali and a FlowMetrix<sup>TM</sup> system were used. Simply because Vignali discloses a type of assay useful for measuring cytokines, and Towaga discloses a particular rat experiment in which cytokines were measured, does not disclose or suggest, or provide motivation or expectation of success for determining particular cytokines to measure and compare in humans, to use as a way to test and evaluate efficacy of treatments for IBS in humans. Perhaps one could analyze the cytokine levels of Towaga with such a system as disclosed in Vignali. However, one would not have arrived at the claimed method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*. Towaga and Vignali together do not suggest or provide motivation or expectation of success for a clinical method, using samples from a biological subject, in which particular cytokine levels are determined and ratios

analyzed, as claimed. The Applicants therefore assert that Towaga and Vignali taken together do not contemplate such a method as claimed.

Therefore, Applicants submit that the disclosure of Towaga in combination with Vignali fails to teach or suggest the claimed invention as amended herein with respect to determining the efficacy of a probiotic in particular, and that one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga and Vignali. Therefore, Applicants assert that the rejection has been overcome.

*Towaga in view of Blumberg*

Claims 6 – 8 have been rejected under 35 USC § 103(a) based on Togawa in view of Blumberg.

As amended herein, Claim 1 is directed to methods of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. Claims 6 – 8 are dependent upon Claim 1 and are therefore affected by this amendment. As the Examiner acknowledges, Towaga teaches administration of TNBS to induce colitis and studies the use of lactoferrin to attenuate the induced colitis. As such, the rejection is now moot since fails to teach or suggest methods to determine the efficacy of probiotics in inflammatory diseases of the bowel.

Additionally, Applicants maintain that Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios. Blumberg also does not suggest establishing or analyzing ratios of cytokines, nor the importance or utility thereof for testing or determining efficacy of a potential treatment. Blumberg simply notes that there is likely an on-going balance between pro- and anti-inflammatory cytokines, and their release and activity in body systems in relation to inflammation. Blumberg is simply a review of known animal models of mucosal inflammation and their *potential* relation to human inflammatory bowel disease. Blumberg merely summarizes which animal models might be better for studying various types of inflammatory bowel disease such as Ulcerative Colitis and Crohn's Disease. However, Blumberg does not suggest or

provide motivation, expectation of success or predictability for the particular claimed methods of evaluating efficacy of treatments.

Therefore, Applicants assert that even if one were to have combined the disclosure of Towaga and Blumberg, one would not have arrived at Applicants' invention, as claimed. Simply because levels of various cytokines can be measured and various experiments can be run in animal models does not provide the requisite motivation or expectation of success for selecting and measuring particular cytokines and monitoring ratios thereof, in humans, for screening and evaluating the efficacy of a potential treatment. Neither Towaga nor Blumberg provide motivation for methods of screening compositions for efficacy in treating diseases of the bowel in humans.

Therefore, Applicants submit that the disclosure of Towaga in combination with Blumberg fails to teach or suggest the claimed invention as amended herein with respect to determining the efficacy of a probiotic in particular, and that one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga and Blumberg. Therefore, Applicants assert that the rejection has been overcome.

*Towaga in view of Bing*

Claims 11 and 12 have been rejected under 35 USC § 103(a) based on Togawa in view of Bing.

As amended herein, Claim 1 is directed to methods of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. Claims 11 and 12 are dependent upon Claim 1 and are therefore affected by this amendment. As the Examiner acknowledges, Towaga teaches administration of TNBS to induce colitis and studies the use of lactoferrin to attenuate the induced colitis. As such, the rejection is now moot since fails to teach or suggest methods to determine the efficacy of probiotics in inflammatory diseases of the bowel.

Additionally, Applicants maintain that Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios, and that one of skill in the art would not have been led by Towaga's rat study to perform a completely different human study. Bing studied stimulated release of various cytokines by PMBCs in patients with UC (ulcerative colitis) compared to healthy controls, and suggested possible reasons for the results, including active disease state, genetic heritage, and medication. Bing looked for correlation between TNF-alpha, IL-6 and sIL-2r production and disease activity, disease location and medication. However, Bing does not suggest or provide motivation, expectation of success or predictability for the particular claimed methods of measuring particular cytokines, measuring cytokine levels in the same subject (versus subjects and controls as in Bing) before and after treatment, and using particular ratios of cytokines in methods of evaluating efficacy of potential treatments. Neither Towaga nor Bing provide the requisite motivation for the Applicants' particular methods. Simply because one *can* measure cytokines, cytokine levels have been measured in various studies, and one *could* in theory calculate various ratios of cytokines, would not have led one of skill in the art to the present invention. The cited documents do not suggest using particular cytokines to screen potential treatments for inflammatory diseases of the bowel, nor provide motivation or expectation of success for developing a screening method for evaluating potential treatments for inflammatory diseases of the bowel.

Therefore, Applicants submit that the disclosure of Towaga in combination with Bing fails to teach or suggest the claimed invention as amended herein with respect to determining the efficacy of a probiotic in particular, and that one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga and Bing. Therefore, Applicants assert that the rejection has been overcome.

Applicants therefore respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 103(a) in view of the amendments to the claims herein.

#### Conclusion

This response represents an earnest effort to place the application in proper form and to distinguish the invention as now claimed from the applied documents. In view of the

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foregoing, reconsideration of this application, entry of the amendments presented herein, withdrawal of the rejections, and allowance of all pending claims is respectfully requested. Early and favorable action in the case is respectfully requested. If the Examiner desires to speak with the Applicants' attorney, the Examiner is invited to please contact the undersigned.

Respectfully submitted,

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